Chiaho Shih

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Academic Appointments

Appointment	Organization
Professor	Pathology and Microbiology & Immunology

Professional Education

Degree	Institution	Field of Study	Graduation Year
	Massachusetts General Hospital, Harvard Medical School	Postgraduate Training	1985
Ph.D.	Massachusetts Institute of Technology		1982
B.S	National Taiwan University		1973

Professional Affiliations

Society	Year(s)
Student Evaluation Committee, NIAID T32 Training Grant on Emerging and Tropical Infectious Diseases	1998
Member, Academic Technology Committee (to review invention and patent applications filed at UTMB)	1997 - 2000
Member, Committee of American Cancer Society Institutional Research Grants	1996 - 1999
WHO Collaboration Center for Tropical Diseases, The University of Texas Medical Branch	1995
Member, Search Committee for faculty of Tropical Disease Center	1994 - 1995

Society	Year(s)
Member, Task Force on Non-AIDS Infectious Diseases and Host Defenses	1994
Member, Admissions Committee, Pathology Graduate Program	1993 - 1995
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Research Interests

Mechanisms of Chronicity of Human Hepatitis B Virus

My research focuses on the mechanisms of chronicity of human hepatitis B virus (HBV) infection, which plays a major role in liver cancer. Specifically, I am studying HBV variants and their biological significance in persistent infection. Three major research projects are outlined below.

Immature Secretion Project (supported by NIH RO1 CA84217): The most frequent mutation of HBV core protein occurs at codon 97 in chronic carriers worldwide. My recent functional characterization of this variant uncovered a novel and strong phenotype, dubbed an "immature secretion" phenotype. Unlike wild type HBV, the secreted virion particles of the codon-97 mutant contain an immature form (lower molecular weight) of the HBV DNA genome. The "immature secretion" phenotype is a global phenomenon since it can be found in both a European strain (ayw) and an Asian strain (adr). Recently, we discovered a naturally occurring mutation, which can offset the immature secretion phenotype. In addition, I uncovered another new phenotype of low level virion secretion associated with naturally occurring mutations at HBcAg codons 5 and 60. Our findings of these predominant secretion-defective variants, including immature secretion and low secretion variants, in more than 80% of HBV replication-positive human hepatoma samples have important implications in liver pathogenesis in chronic hepatitis B patients. In addition, these secretion-defective capsid variants provide an important tool for studying the regulation of HBV virion assembly and morphogenesis.

DI Particle Project (supported by NIH RO1 CA70336): Since the original discovery of defective interfering (DI) variants of influenza virus in tissue culture in 1947, there have been no reports that DI variants of animal viruses can be found in natural infections. For the past half a century, DI research has been limited to laboratory settings (tissue culture and animal models), despite the fact that it is generally believed that DI particles are important for chronicity and pathogenesis in viral diseases.

Using a novel approach, I discovered the first DI variants in human natural

infections. The results have renewed research interests in DI variants, which might be involved in a number of human chronic progressive viral diseases. This project is to test the hypothesis that HBV DI particles can influence liver pathogenesis as well as contribute to the establishment of chronic infection. In addition to investigating the mechanism of HBV defective interference, I am extending the HBV pathogenesis study to the woodchuck model.

Inducible Replication of Hepatitis B Virus in Trans-differentiated Pancreatic Hepatocytes: Despite the existence of a large number of hepatoma cell lines, only a very limited number of cell lines (HepG2, Huh7 and rat hepatoma 7777) are currently available to support the efficient replication of HBV. Recently, both pancreatic buds from mouse embryo and a rat pancreatic cell line was shown to transdifferentiate to liver-like cells upon induction with steroid and cytokines. To determine if the hepatotropic HBV can indeed replicate in transdifferentiated pancreatic hepatocytes, we stably transfected this pancreatic cell line with HBV DNA, and viral activities were characterized with or without induction. A full spectrum of HBV replicative intermediates, including covalently closed circular (ccc) DNA, can be detected in this system. HBcAg and HBsAg can be detected by ELISA, Western blot and immunofluorescence microscopy. Predominant nuclear localization of HBcAg was observed when the culture was aged. Interestingly, while the expression of HBsAg was inducer dependent, the expression of HBeAg was age dependent. Characteristic Dane particles and subviral particles were identified by electron microscopy. Since core specific RNA can be detected without induction by Northern and primer extension analysis, a post-transcriptional control of the expression of HBV core antigen is being investigated. In summary, HBV replication and gene expression can be induced synchronously and maintained by physiological inducers in a tissue culture model of transdifferentiation. This novel system offers an opportunity for drug screening and molecular dissection of virus-host interaction.

Selected Publications

1. Shih, C and Yuan, T.T. "A cis/trans Genetic Test for Pleiotropic Phenotypes Associated with a Frequent Naturally Occurring Mutation at Amino Acid 97 of HBV Core Protein". Methods Mol Med. 95:247-257, 2004
2. Shih, C and Yuan, T.T. "A One-filter-three-probe Assay for Defective Interference (DI) Effects of Naturally-Occurring Core Internal Deletion (CID) Variants of Human Hepatitis B Virus". Methods Mol Med. 2004;95:151-163, 2004.
3. Shih, C and Tai, P.C. "Detection of Hypermodified Middle-Envelope (M) Proteins Secreted from Naturally Occurring HBV Variants Containing a preS2 Internal Deletion". Methods Mol Med. 95:165-173, 2004
4. Chua, P.K., Wen, Y.M., and Shih, C. Co-existence of Two Distinct Secretion Mutations (P5T and I97L) in Hepatitis B Virus Core Produces Wild Type Secretion. J. Virol. 77:7673-7676, 2003

5. Newman, M., Suk, F.M., Cajimat, M., Chua, P.K.,and Shih, C. Stability and Morphology Comparisons of Self-assembled Virus-Like Particles from Wild Type and Mutant Human Hepatitis B Virus Capsid Proteins. J. Virol. 77:12950-12960, 2003
6. Le Pogam S.and Shih, C. Immature secretion of hepatitis B virions regulated by intermolecular side-chain interaction between core and preS1 envelope proteins. J. Virol. 76:6510-6517, 2002. (recommended in the paid website facultyof1000.com)
7. Suk, F.M., Lin, M.H., Newman, M., Pan, S., Chen, S.H., Liu, J.D.,and Shih, C. Replication Advantage and Host Factor Independent Phenotypes Attributable to a Common Naturally Occurring Capsid Mutation (I97L) in Human Hepatitis B Virus. J. Virol. 76:12069-12077, 2002. (abstracted by CSA in Virology & AIDS Abstracts database)
8. Sahu, G.K., Tai, P.C., Banerjee, S., Lin, M.H., Tennant, B., Gerin, J., and Shih, C. Out-of-frame vs. in-frame core internal deletion (CID) variants of human and woodchuck hepatitis B viruses. Virology 292:35-43, 2002 (published online in December, 2001)
9. Tai, P-C, Suk, F.M., Gerlich W., Neurath R., and Shih, C. Hypermodification of an internally deleted middle envelope (M) protein of frequent and predominant hepatitis B virus variants. Virology 292:44-58, 2002 (published online in December, 2001) (featured on frontcover).
10. Yuan T.T. and Shih, C. A frequent naturally occurring mutation P130T of human hepatitis B virus core antigen is compensatory for the immature secretion phenotype of another frequent variant F97L. J. Virol. 74: 4929-4932, 2000
11. Le Pogam S., Yuan T.T., Sahu G.K., Chatterjee S., and Shih, C. Low-level secretion of human hepatitis B virus virions caused by two independent, naturally occurring mutations (P5T and L60V) in the capsid protein. J. Virol. 74: 9099-9105, 2000
12. Yuan, T.T., Sahu, G. K., Whitehead, W. E., Greenberg, R., and Shih, C. The Mechanism of an "Immature Secretion" Phenotype of a Highly Frequent Naturally Occurring Missense Mutation at Codon 97 of Human Hepatitis B Virus Core Antigen. J Virol 73: 5731-5740, 1999
13. Yuan, T.T., Tai, P.C., and Shih, C. Subtype-independent immature secretion and subtype-dependent replication deficiency of a highly frequent naturally occurring mutation of human hepatitis B virus core antigen. J. Virol. 73: 10122-10128, 1999
14. Yuan, T.T., Lin, M.H., Chen, D.S., and Shih, C. A defective interference-like phenomenon of human hepatitis B virus in chronic carriers. J Virol 72: 578-584, 1998
15. Yuan, T.T., Lin, M.H., Qiu, S.M., and Shih, C. Functional characterization of naturally-occurring variants of human hepatitis B virus containing the core internal deletion mutation. J Virol 72: 2168-2176, 1998
16. Tai P-C, Banik D, Lin G-I, Pai S, Pai K, Lin M-H, Yuoh G, Che S, Hsu SH, Chen T-C, Kuo T, Lee C-S, Yang C-S, Shih C. Novel and frequent

mutations of hepatitis B virus coincide with an MHC class I-restricted T cell epitope of the surface antigen. J Virol 71: 4852-4856, 1997
17. Yuan T-T, Faruqi A, Shih JWK, Shih C. The mechanism of natural occurrence of two closely-linked HBV precore predominant mutations. Virology 211: 144-156, 1995.
18. Hosono S, Tai P-C, Wang W, Ambrose M, Hwang DG-Y, Yuan T-T, Peng B-H, Yang C-S, Lee C-S, Shih C. Core antigen mutations of human hepatitis B virus in hepatomas accumulate in MHC class II-restricted T cell epitopes. Virology 212: 151-162, 1995.
19. Wu KJ, Wilson DR, Shih C, Darlington GJ. The transcription factor HNFl acts with C/EBP alpha to synergistically activate the human albumin promoter through a novel HNFl protein domain. J Biol Chem 269: 1177-1182, 1994
20. Hosono S, Chou MJ, Lee CS, Shih C. Infrequent mutation of p53 gene in hepatitis B virus positive primary hepatocellular carcinomas. Oncogene 8: 491-496, 1993
21. Pei D, Shih C. An `attenuator domain' is sandwiched by two distinct transactivation domains in the transcription factor C/EBP. Mol Cell Biol 11: 1480 1487, 1991
22. Hosono S, Lee CS, Chou MJ, Yang CS, Shih C. Molecular analysis of the p53 alleles in primary hepatocellular carcinomas and cell lines. Oncogene 6: 237 243, 1991
23. Roychoudhury S, Faruqi A, Shih C. Pregenomic RNA encapsidation analysis of eleven missense and nonsense polymerase mutants of human hepatitis B virus. J Virol 65: 3617 3624, 1991
24. Faruqi A, Roychoudhury S, Greenberg R, Israel J, Shih C. Replication defective missense mutations within the terminal protein and spacer/intron regions of the polymerase gene of human hepatitis B virus. Virology 183: 764-768, 1991
25. Pei D, Shih C. Transcriptional activation and repression by a cellular DNA binding protein C/EBP. J Virol 64: 1517 1522, 1990
26. Roychoudhury S, Shih C. cis rescue of a mutated reverse transcriptase gene of human hepatitis B virus by creation of an internal ATG. J Virol 64: 1063 1069, 1990
27. Ou J, Bao H, Shih C, Tahara SM. Preferred translation of human hepatitis B virus polymerase from core protein but not precore protein specific transcript. J Virol 64: 4578 4581, 1990
28. Shih C, Yu MYW, Li LS, Shih JWK. Hepatitis B virus propagated in a rat hepatoma cell line is infectious in a primate model. Virology 179: 871 873, 1990
29. Shih C, Li LS, Roychoudhury S, Ho MH. In vitro propagation of human hepatitis B virus in a rat hepatoma cell line. Proc Natl Acad Sci USA 86: 6223 6327, 1989
30. Shih C, Burke K, Zeldis J, Wands J, Isselbacher KJ, Chou MJ, Yang CS, Lee CS, Goodman HM. Tight clustering of human hepatitis B virus

integration sites in hepatomas near a 'triple stranded' region. J Virol 61: 3491 3498, 1987
31. Lun H, Isselbacher KJ, Wands JR, Goodman HM, Shih C, Quarone A. Establishment and characterization of a new human hepatocellular carcinoma cell line. In Vitro 20: 493 504, 1984
32. Parada LF, Shih C, Murray M, Weinberg RA. The oncogene of a human bladder carcinoma. In: Progress in Nucleic Acid Research and Molecular Biology 29: 269 272, 1983
33. Parada LF, Tabin CJ, Shih C, Weinberg RA. Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus ras gene. Nature 297: 474 479, 1983
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35. Shih C, Weinberg RA. Isolation of a transforming sequence from a human bladder carcinoma cell line. Cell 29: 161 169, 1982
36. Padhy LC, Shih C, Cowing D, Finkelstein RJ, Weinberg RA. Identification of a phosphoprotein specifically induced by the transforming DNA of rat neuroblastoma. Cell 28: 865-871, 1982
37. Shih C, Padhy LC, Murray M, Weinberg RA. Transforming genes of carcinomas and neuroblastoma introduced into mouse fibroblasts. Nature 290: 261 264, 1981
38. Murray MJ, Shilo BZ, Shih C, Cowing D, Hsu HW, Weinberg RA. Three different human tumor cell lines contain different oncogenes. Cell 25: 355 361, 1981
39. Shih C, Shilo B, Goldfarb MP, Dannenberg A, Weinberg RA. Passage of phenotypes of chemically transformed cells via transfection of DNA and chromatin. Proc Nat Acad Sci 79: 5714 5718, 1979
40. Sun TT, Shih C, Green H. Keratin cytoskeletons in epithelial cells of internal organs. Proc Nat Acad Sci 6: 2813 2817, 1979